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(21) International Application Number: PCT/CA93/00302 (22) International Filing Date: 27 July 1993 (27.07.93) (30) Priority data: 07/919,252 27 July 1992 (27.07.92) US (71) Applicant: HAEMACURE BIOTECH INC. [CA/CA]; 245, boul. Hymus, Pointe-Claire, Quebec H9R 1G6 (CA). (72) Inventor: BRODNIEWICZ, Teresa ; 3067, Murray, Chomedey, Laval, Quebec H7V 2H2 (CA). (74) Agent: PRINCE, Gaëtan; Goudreau Gage Dubuc & Marti- neau Walker, 800, place Victoria, Suite 3400, P.O. Box 242, Montreal, Quebec H4Z 1E9 (CA).		(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: BIOCOMPATIBLE SURGICAL IMPLANT (57) Abstract The invention provides a biocompatible surgical implant particularly useful for breast or testicular reconstruction or augmentation comprising a stabilized fibrin semisolid, optionally sealed in a shaped shell. Preferred starting material for production of the implant is whole plasma from autologous or homologous donation, concentrated with respect to fibrinogen.		

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TITLE

BIOCOMPATIBLE SURGICAL IMPLANT

FIELD OF THE INVENTION

5 The invention relates to biocompatible implants or prostheses for use in soft tissue remodelling, especially for cosmetic surgery or post-surgical or post-traumatic reconstruction. In particular, the invention relates to a biocompatible implant for breast or testicle reconstruction or augmentation.

10 **DESCRIPTION OF THE RELATED ART**

Contemporary breast implants typically comprise appropriately shaped shells or envelopes of a synthetic plastic encasing a filler material. An early filler material, physiological saline, proved to be
15 cosmetically unsatisfactory owing to its low viscosity, and has been widely replaced by fillers comprising solids, semisolids, gels, or liquids of higher viscosity which more nearly approximate the physical properties of the human breast. Foamed rubber (U.S. Patent
20 3,795,921); synthetic resins such as polyvinylpyrrolidone, polyisocyanate, polyvinyl alcohol, polyvinyl esters, polyamides, polyurethanes, polymerized hydrocarbons, and polyvinylchloride (U.S. Patents

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4,147,085, 4,787,905 and 5,067,965); vegetable oils such as peanut or sunflower seed oil; plasticized starch gel (U.S. Patent 4,612,009); and interconnected cells (U.S. Patent 4,507,810) are exemplary. However, for many years the filler material of choice for breast implants has been silicone oil or gel. While generally more cosmetically suitable than saline, these and other implant filler materials incompatible with the human body pose a definite clinical hazard if the shell containing the filler disintegrates or ruptures with leakage of the contents, a relatively common occurrence. Documented reactions of mammals exposed to exogenous implant materials include inflammation, edemas, foreign body cysts, granulomas, fibrosis, and, most recently in the case of silicone gels, autoimmune disease.

SUMMARY OF THE INVENTION

The invention provides an implant for soft tissue reconstruction or augmentation, particularly a breast or testicle implant, comprising a semisolid of crosslinked fibrin strands of the desired cosmetic characteristics for the intended application. The fibrin semisolid is conveniently obtained by coagulation of the plasma fraction enriched in fibrinogen and containing plasma factors necessary for coagulation, derived from blood

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preferably autologous or homologous to the implant recipient to avoid introduction of immunogenic foreign proteins into the body. For optimal results, the starting plasma fraction is substantially devoid of
5 proteolytic enzymes or other blood components which might contribute to deterioration of the product or inhibit its production. This is accomplished by procedures known in the art.

The fibrin semisolid of the invention may be used
10 per se as the implant, or may be contoured as cosmetically desirable and/or encased in a conventional shell or envelope for implantation, for example to inhibit any possible resorption of the implant. The product may include one or more components as desired to
15 modify the physical or chemical characteristics of the final product.

In contrast to known implant materials such as saline the fibrin semisolid of the invention has excellent cosmetic properties, particularly
20 contourability and flexibility combined with strength, coupled with little or no potential toxicity such as that associated with silicone gels. The product is readily tailored for the cosmetic needs of the individual recipient by varying the amounts of
25 coagulation factors employed, and/or additives, and has

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the advantage of not requiring a shell or envelope inimicable to the human body as a shield against toxic reaction of the body to the implant.

DETAILED DESCRIPTION OF THE INVENTION

5 The stabilized fibrin semisolid of the invention is prepared under physiological conditions from an aqueous solution essentially containing solubilized fibrinogen and effective amounts of plasma factors known to be required for converting fibrinogen to a semisolid
10 crosslinked fibrin polymer having the desired physical characteristics. The product is stabilized by removal or inactivation of any proteolytic (particularly fibrinolytic) enzymes present, or other components which might contribute to biodegradation of the product,
15 either prior to implant or as implanted, and is preferably sterilized prior to use to inactivate or remove any potentially deleterious materials present.

 As known in the art, fibrinogen, a soluble plasma protein, is readily converted in vitro in aqueous
20 solution under physiological conditions to fibrin, an insoluble polymer. The reaction proceeds in the presence of thrombin (a proteolytic enzyme which cleaves small polypeptides from the fibrinogen molecule to produce fibrin monomer and also activates factor XIII,

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fibrin stabilizing factor) and factor XIII (which functions as a crosslinking agent to stabilize the resulting fibrin polymer against biodegradation), according to the following mechanism:

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5      fibrin stabilizing
      thrombin      factor (factor XIII)
fibrinogen -----> fibrin monomer, ----->
                    fibrinopeptides  Ca++ (factor IV)

fibrin polymer + fibrinopeptides

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10 Calcium ions, which participate in vivo, are not essential to the in vitro reaction, but contribution per se or as equivalents to the structure of the product as described below.

Under non-denaturing conditions, clottable
15 fibrinogen is readily converted according to this
mechanism to a semisolid of insoluble fibrin polymer
suitable for use in the practice of the invention. In
general, clottable fibrinogen is readily converted in
vitro in aqueous solution under conditions of reaction
20 comprising a pH of from about 6.5 to about 8, at room
temperature and pressure; temperatures of from about
10°C to about 40°C are suitable, and about 20°C is
particularly recommended.

In one embodiment of the invention, to produce the
25 stabilized crosslinked fibrin semisolid product of the
invention, an aqueous polymerization solution is made

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up, broadly containing sufficient clottable fibrinogen (herein referred to as "fibrinogen") as measured by a standard method, such as the method of Clauss described in Acta Haematol. 17:237; 1957 to obtain a product of the desired size. Thrombin, factor XIII, and optional cations such as calcium ions or other cocrosslinking agent for crosslinking of the polymer, are included in sufficient amounts to substantially convert the clottable fibrinogen to fibrin monomer, polymerize the monomer, and crosslink the fibrin polymer to a product of the desired physical characteristics. The fibrinogen/thrombin/factor XIII ratio and the amount of the optional cocrosslinking agent(s) are controlled for the individual application to provide a physically stable semisolid product of the desired tensile strength, elasticity (flexibility), or other physical characteristics for the intended use. Any components present which might contribute to biodegradation of the product are removed or inactivated to the extent feasible or necessary to provide a biochemically stable semisolid product. In general, a sufficient amount of thrombin is provided to substantially monomerize clottable fibrinogen present measured as described above and to activate factor XIII present to provide a semisolid crosslinked fibrin polymer of adequate

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strength and structural stability for the intended use, most preferably having a flexibility approximating that of the natural tissue it is replacing or augmenting. Cocrosslinking agents such as calcium ions are included
5 as necessary or desirable to obtain a product of the desired physical characteristics. Excessive amounts of thrombin/factor XIII/cocrosslinking agent are undesirable, as the product will toughen and lack flexibility. Conversely, insufficient amounts of
10 thrombin/factor XIII/cocrosslinking agent are undesirable, as the product will lack cohesiveness, strength, and stability. In an exemplary embodiment, ratios of fibrinogen/thrombin for most applications are from about 2 to 150 mg fibrinogen to about 1 to 1000 IU
15 (International Units) of thrombin, based on a factor XIII ratio of from about 0.01 to 250 units of factor XIII.

The quantity of fibrinogen, thrombin, factor XIII and any cocrosslinking agent such as calcium ion is
20 varied as described above to provide a cosmetically suitable product of a strength and flexibility adapted to individual needs.

In an exemplary embodiment, a semisolid fibrin product according to the invention useful for breast or
25 generic implantation is characterized by sufficient

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deformability to provide a Precision Penetrometer reading of about 180. The instrument comprises a weighted probe which is dropped from a standard height into a standardized amount of test material; deformation of the product over time is reflected by the reading obtained. The instrument is available from the Precision Scientific Petroleum Instruments Co., Bellwood, IL (USA). Implant characteristics may be matched by providing a product of comparable size and thickness having closely similar deformity as measured by the Precision Penetrometer or comparable instrument, with appropriate sizing and contouring.

In general, depending upon the desired physical characteristics of the product, the aqueous polymerization solution with no non-essential additives contains 1) at least about 2 mg of fibrinogen per ml of water (preferably distilled or deionized water), and preferably at least about 20 mg of fibrinogen per ml of water, up to about 150 mg fibrinogen per ml of water; 2) at least about 2 IU to about 1000 IU thrombin per ml water fibrinogen solution, or an amount sufficient to substantially polymerize available fibrin monomer; and 3) at least about 0.4 units of factor XIII per 100 mg of fibrinogen, or at least an amount sufficient to substantially stabilize the resultant polymer. The

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solution may also contain additives in addition to materials noted, with adjustment of the amounts of fibrinogen, thrombin, factor XIII, and any cocrosslinking agent, as necessary.

5 As noted above, calcium ions are not essential to the polymerization reaction; however, calcium ions or other cocrosslinking agent such as divalent alkaline earth metal cations promote crosslinking of the fibrin polymer as known in the art and preferably are added in
10 the amount sufficient to rigidify the product to the extent desired. Suitable sources of calcium or other cations include any salts of these cations having good water-solubility wherein the anion is substantially neutral in the polymerization reaction, such as calcium
15 chloride. Addition of calcium chloride to the above-described polymerization solution containing fibrinogen, thrombin, and factor XIII to provide an about 0.1 to 50 mM solution of CaCl_2 is exemplary.

20 The starting materials fibrinogen, thrombin and factor XIII are readily available commercially. Human or bovine fibrinogen and thrombin suitable for use in the practice of the invention are available from Calbiochem, San Diego, CA (USA) and factor XIII from American Diagnostics, Inc., Greenwich, CT, USA.

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If desired, the aqueous polymerization solution, containing fibrinogen, thrombin, factor XIII and optional Ca^{++} or other cocrosslinking agent also may contain, for example, solid or semisolid particulates for entrapment into the fibrin polymer as it forms for modification of the physical characteristics of the product, such as naturally-occurring proteins including collagen, albumin, or immunoglobulin; any such proteins are preferably autologous to the implant recipient to avoid immunogenic effects. The polymerization solution may also contain other additives for incorporation into the product which contribute to its physical or chemical characteristics such as bubbles of entrapped gas, e.g., nitrogen, or additives such as signal enhancers to facilitate subsequent mammography screenings in the instance of breast implant. Other additives as useful may be incorporated into the product, at any stage of the process.

In the preferred procedure, the polymerized fibrin monomer (fibrin coagulate or semisolid) of the invention is derived from whole plasma obtained by autologous or homologous donation from a human, although any suitable plasma, including that from heterologous donation, can be used as starting material. The plasma is collected into anticoagulant by customary methods and treated

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preferably under sterile conditions to remove plasminogen (a fibrinolytic enzyme) and concentrate fibrinogen and factor XIII. The resulting fibrinogen-enriched fraction, depleted of plasminogen, is then
5 coagulated with thrombin and optional cocrosslinking agent to produce the stabilized fibrin polymeric semisolid of the invention.

In the best mode of the invention as presently known, human autologous or homologous plasma
10 cryoprecipitate or ethanocryoprecipitate obtained by deep-freezing and thawing of collected plasma as known in the art is employed as starting material to produce the semisolid fibrin product of the invention. Useful standard cryoprecipitate generally mainly comprises
15 plasma proteins fibrinogen, fibronectin, factor VIII complex, and factor XIII; albumin, plasminogen, and immunoglobulins may also be present in this fraction.

The starting cryoprecipitate is obtainable from plasma fractionation centers, or may be produced in
20 local laboratories, particularly in the case of autologous plasma. Starting cryoprecipitate is then preferably treated to concentrate fibrinogen and factor XIII and remove plasminogen, for example by resuspension of the cryoprecipitate in plasma or buffer
25 (e.g., Tris buffered saline comprising about 0.04 M Tris

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and about 0.15 M NaCl) followed by adsorption on lysine-Sepharose (Pharmacia, Uppsala, Sweden) to remove plasminogen. Alternatively, collected plasma may be first purified by affinity chromatography as above to
5 remove plasminogen, and then cryoprecipitated as described above.

These or other purification procedures are repeated as necessary both to increase concentration of fibrinogen and factor XIII to provide solution
10 concentrations of these clotting components as described above, and to substantially remove any plasma components present which would be deleterious to the polymerization of the fibrin monomer or to the product, particularly fibrinolytic or other proteolytic enzymes such as
15 plasminogen; preferably, plasma proteins extraneous to the product such as immunoglobulins are also removed to the extent economically feasible. Further, product fibrinogen solution obtained from whole plasma is preferably additionally stabilized prior to the
20 coagulation against enzymatic degradation of essential proteins by addition of a suitable proteolytic enzyme inhibitor such as Trasylol (Sigma Chemical, MO, USA). Broadly, for use in the practice of the invention, depending upon the application, plasma-derived purified
25 fibrinogen solution preferably contains fibrinogen and

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factor XIII in the amounts described above, and is substantially devoid of active plasma components present which are deleterious to the desired implant properties, to produce a semisolid fibrin strands stabilized against biodegradation for long-term life in the intended environment.

To coagulate, the plasma-derived purified fibrinogen solution from above is mixed with thrombin from a suitable source (e.g., bovine or human thrombin) and optionally calcium ions or other cocrosslinking agent under non-denaturing conditions. The fibrinogen rapidly coagulates or polymerizes to fibrin, forming the semisolid of fibrin strands of the invention. The coagulate is then allowed to stand for a period of time sufficient to permit customary contraction and exudation of liquid, usually for about 6 to 24 hours.

At any stage, product obtained by non-autologous donation is preferably treated to inactivate any viral material present, as by solvent/detergent or pasteurisation methods known in the art (see, e.g., U.S. Patents 4,540,573; 4,764,363; 4,820,805; or European Patent EP 0,131,740) which do not significantly affect the activity of clotting factors essential to the invention. Whatever process is employed, the entire

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process is preferably carried out under sterile conditions.

Fibrin product obtained by any suitable process may be employed according to the invention as implant per se or placed in an appropriately shaped envelope or shell under sterile conditions and sealed. The product may be contoured as appropriate during any stage of the process. In order to preserve the structure of the material and ensure inactivation of any enzymes or possible viruses, the implant is preferably treated prior to use, whether or not encased in a shell, as by heat and/or irradiation or, for example, by glutaraldehyde or formaldehyde. A recommended heat treatment comprises exposure of the product to a temperature of from about 60°C to about 105°C for a period of time ranging from about 1 min to about 200 hours. Irradiation is effective at dosages from about 5 to 100 kGrays.

For clinical use, the fibrin semisolid product of the invention is implanted in the body by surgical methods known in the art, for example, those conventionally employed for the surgical implant of silicone gels.

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EXAMPLE 1

Plasma from autologous donation is collected and submitted to affinity chromatography on a lysine-Sepharose column (Pharmacia-Uppsala, Sweden), in order to remove plasminogen. The obtained effluent is deep-frozen for at least 6 hours and cryoprecipitate is obtained by slow thawing of the plasma at a temperature of below 10°C. Thus obtained cryoprecipitate is harvested by centrifugation at the temperature below 10°C, washed twice with citrated saline and resuspended in Tris buffered saline at concentration of 45 mg of fibrogen/ml of the buffer. To this solution a protease inhibitor (for example, Trasylol, Sigma, Missouri, U.S.A.) is added at a concentration of 10 000 of KIU/ml of the product. The solution is sterile filtered and coagulated under sterile conditions by the addition of 50 I.U. of human thrombin in 50 mM CaCl₂.

The resulting coagulated material is submitted to incubation for a period of 6 hours at 37°C and heat-treated at 70°C for a period of 100 hours in a sealed container. After this procedure, the solid implant is taken, placed in a plastic shell and sealed according to the known technique. The obtained implant is irradiated by 80 kGrays and ready for the implantation.

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EXAMPLE 2

Plasma obtained from homologous donation is deep frozen for a period of 6 hours. The plasma is thawed and warmed to a temperature of 30°C. Following this the plasma is cooled to a temperature of 0°C and precooled ethanol at a concentration of 10% is added to it. The solution is slowly mixed overnight at 0°C. The next day ethanocryoprecipitate is harvested by centrifugation, washed twice with citrated buffer and resuspended in buffer containing 0.02 M Tris and 0.15 M NaCl pH 7.1. The solution is submitted to affinity chromatography on lysine-Sepharose in order to remove plasminogen. The resulting effluent is submitted to an antiviral treatment such as solvent/detergent (Tri-n-butyl phosphate/Tween 20) for a period of 6 hours at 30°C. Viral inactivation is followed by double reprecipitation in the cold 10% ethanol as described in Example 1 and by extensive washing.

The resulting precipitate is recovered, resuspended in a concentration of 60 mg of fibrinogen/ml of Tris-saline containing Trasylol (15 000 K.I.U.). The product is sterile filtered and coagulated by 20 Units of thrombin in 0.025 M CaCl₂. The product is incubated overnight at 37°C, then sealed, and subjected to heat treated at 80° for 72 hours and gamma irradiation of 100

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kGrays. The product is implanted without encasing in a plastic shell.

EXAMPLE 3

Commercial human fibrinogen (Calbiochem) is
5 resuspended in a concentration of 55 mg of fibrinogen/ml
of buffered saline, factor XIII is added in the quantity
of 30 units/ml and human albumin in a concentration of
5 mg/ml. The product is submitted to viral inactivation
by solvent/detergent (Tri-n-butyl-phosphate and Triton)
10 for a period of 10 hours at 37°C; this is followed by
affinity chromatography removal of residual plasminogen
and solvent/detergent mixture.

The resulting solution is sterile filtered and
coagulated by the addition of bovine thrombin in a
15 concentration of 15 units/ml of the product under
sterile conditions. The product is incubated at 30°C
for 10 hours and then heated at 70°C for a period of 100
hours. The excluded solution is removed and the
product, after encasing in a plastic shell, is submitted
20 to 90 kGrays of gamma irradiation. The thus-obtained
product is ready for implantation.

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The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. An article of manufacture comprising a fibrin
5 semisolid surgical implant of stabilized fibrin strands for soft tissue reconstruction or augmentation.
2. The article of Claim 1, wherein the fibrin semisolid implant is produced by polymerization of fibrin monomer from an aqueous fibrinogen solution
10 containing at least about 2 mg/ml fibrinogen.
3. The article of Claim 2, wherein the fibrin semisolid implant is produced from a fibrinogen solution containing at least about 2.0 mg/ml fibrinogen up to about 150 mg/ml fibrinogen.
- 15 4. The article of Claim 3, wherein the fibrinogen solution contains fibrinogen, thrombin and factor XIII in amounts of about 1 to 1 000 IU thrombin per about 2 to 150 mg fibrinogen and about 0.01 to 250 units factor XIII.

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5. The article of Claim 1, wherein the fibrin semisolid is produced from a plasma fraction consisting essentially of fibrinogen, thrombin and factor XIII in amounts sufficient to convert fibrinogen to fibrin and
5 stabilize the product to the desired physical characteristics.

6. The article of Claim 5, wherein the plasma fraction contains fibrinogen, thrombin and factor XIII in amounts of about 1 to 1 000 IU thrombin per about 2 to 150 mg
10 fibrinogen and about 0.01 to 250 units factor XIII.

7. The article of Claim 3, wherein the fibrinogen solution further contains a cocrosslinking agent.

8. The article of Claim 4, wherein the fibrinogen solution further contains a cocrosslinking agent
15 comprising a water-soluble salt of an alkaline earth metal.

9. The article of Claim 8, wherein the cocrosslinking agent is calcium chloride present in an amount sufficient to provide a fibrinogen solution of about 0.1
20 to 50 mM CaCl_2 .

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10. The article of Claim 5, wherein the plasma fraction further contains a cocrosslinking agent.

11. The article of Claim 6, wherein the plasma fraction further contains a cocrosslinking agent comprising a
5 water-soluble salt of an alkaline earth metal.

12. The article of Claim 11, wherein the cocrosslinking agent is calcium chloride present in an amount sufficient to provide a plasma fraction of about 0.01 to 50 mM CaCl_2 .

10 13. The article of Claim 5, wherein the fibrin strands are stabilized by crosslinkage and by removal or inactivation of enzymes present in the plasma fraction.

14. The article of any one of Claims 5, 6, 10, 11 and 12 wherein the plasma is autologous or homologous with
15 an implant recipient.

15. The article of Claim 1, adapted for breast or testicle reconstruction or augmentation.

16. The implant of Claim 5, adapted for breast or testicle reconstruction or augmentation.

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17. The article of Claim 1, contoured in the form of a breast or testicle.

18. The article of Claim 1, wherein said implant is sealed in a shell.

5 19. The article of Claim 16, wherein said implant is sealed in a shell.

20. A method for producing the article of Claim 5, comprising purifying whole plasma to obtain a purified plasma fraction enriched with respect to fibrinogen and
10 factor XIII, and adding thrombin and optionally cocrosslinking agent to the purified fraction in amounts sufficient to convert fibrinogen to fibrin.

21. The method of Claim 20, wherein the purified plasma fraction is obtained by a process including
15 cryoprecipitation from whole plasma.

22. The method of Claim 20, wherein the enriched plasma fraction consists essentially of fibrinogen, factor XIII and one or more proteolytic enzyme inhibitors.

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23. The method of Claim 20, wherein the enriched plasma fraction is depleted with respect to plasminogen.

24. The method of Claim 22, wherein the enriched plasma fraction is depleted with respect to plasminogen.

5 25. The method of Claim 20, wherein the whole plasma is autologous or homologous to an implant recipient.

26. A method for reconstruction or augmenting soft tissue in a mammal comprising surgically implanting the article of Claim 1 in a recipient.

10 27. The method of Claim 26, wherein the fibrin semisolid is produced from a plasma fraction comprising fibrinogen, thrombin, factor XIII and optional cocrosslinking agent in amounts sufficient to convert fibrinogen to fibrin and stabilize the product.

15 28. The method of Claim 27, wherein the cocrosslinking agent is calcium ion.

29. The method of Claim 27, wherein the plasma is autologous or homologous to an implant recipient.

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30. The method of Claim 20, wherein the article is sterilized prior to use.

31. The article of Claim 1 having a reading of about 100 - 250 measured by a Precision Penetrometer.

5 32. The article of Claim 31 having a reading of about 180 measured by a Precision Penetrometer.

33. The article of Claim 1, structurally stabilized prior to use.

10 34. An article of manufacture comprising a fibrin semisolid of stabilized fibrin strands, said article being adapted or shaped to be used as a permanent implant for soft tissue reconstruction or augmentation.

35. The article of claim 34 containing at least about 2 mg/cc fibrin.

15 36. The article of claim 35, containing at least about 2.0 mg/cc fibrin up to 150 mg/cc fibrin.

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37. The article of claim 34 wherein said soft tissue is selected from the group consisting of breast and testicle.

38. The article of claim 34 wherein said semisolid is
5 sealed in a shell prior to use as an implant.

39. The article of claim 34 having deformability measured by a reading of about 100- 250 on a Precision Penetrometer.

40. The article of claim 39 having a deformability
10 measured by a reading of about 180 on a Precision Penetrometer.

41. The article of claim 34, further structurally stabilized prior to use by heat treatment, radiation, formaldehyde or glutaraldehyde.

42. The article of claim 34 further containing proteins
15 selected from the group consisting of collagen, albumin and fibronectin.

43. The article of Claim 34 further containing bubbles of gas entrapped in said semisolid.

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44. The article of claim 43 wherein said gas is nitrogen.

45. The article of claim 34 further containing signal enhancers for facilitating radiography of said implant.

5 46. In a soft tissue implant containing a filling material encased in a shell, the improvement consisting of replacing said filling material by a semisolid comprising stabilized fibrin strands.

10 47. The improvement of claim 46, wherein said soft tissue is breast tissue.

48. The improvement of claim 46, wherein said soft tissue is testicle tissue.

49. The article of claim 34 further containing aprotinin in an amount of about 10 000 KIU/cc.

INTERNATIONAL SEARCH REPORT

Intern al Application No

PCT/CA 93/00302

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 A61L27/00 //A61F2/12,A61F2/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 166 263 (GREEN CROSS) 2 January 1986 see claims 1,8 ---	1
A	WO,A,86 01814 (THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK) 27 March 1986 see claims 1-34; figure 1 ---	1-49
A	EP,A,0 305 243 (CENTRE REGIONAL DE TRANSFUSION SANGUINE DE LILLE) 1 March 1989 see page 7, line 24 - line 46; claims 1-22 -----	1



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Information on patent family members

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